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<p>(21) International Application Number: PCT/US91/04381 (22) International Filing Date: 27 June 1991 (27.06.91) (30) Priority data: 548,825 6 July 1990 (06.07.90) US (71) Applicant: THE DU PONT MERCK PHARMACEUTICAL COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US). (72) Inventors: BEHRENS, Carl, Henry ; 60 Beech Hill Drive, Newark, DE 19711 (US). JAFFEE, Bruce, Donald ; 3206 Heathwood Road, Wilmington, DE 19810 (US). (74) Agents: FERGUSON, Blair, Q. et al.; The Du Pont Merck Pharmaceutical Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).</p>		<p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: 3-PHENYL-5,6-DIHYDROBENZ[C]ACRIDINE-7-CARBOXYLIC ACIDS AND RELATED COMPOUNDS AS IMMUNOSUPPRESSIVE AGENTS (57) Abstract Dihydrobenz[c]acridine carboxylic acid derivatives are provided which are useful for the treatment and/or prevention of organ transplantation rejection, graft versus host disease, autoimmune diseases, psoriasis and chronic inflammatory diseases.</p>		

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TITLE

3-Phenyl-5,6-dihydrobenz[c]acridine-7-Carboxylic Acids
and Related Compounds as Immunosuppressive Agents

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FIELD OF THE INVENTION

This invention relates to methods for the treatment
and/or prevention of organ transplantation rejection,
graft versus host disease, autoimmune diseases, and
chronic inflammatory disease and more particularly to
10 methods of treating such diseases with 3-phenyl-5,6-
dihydrobenz[c]acridine-7-carboxylic acids and
derivatives thereof.

BACKGROUND OF THE INVENTION

Copending and commonly assigned U.S. Patent
15 Applications Serial Number 07/301,379 and Serial Number
07/473,507 (Behrens) describe 3-phenyl-5,6-
dihydrobenz[c]acridine-7-carboxylic acids and their
derivatives as tumor inhibiting agents.

It has now been found that the compounds described
20 in USSN 07/301,379 and 07/473,507 are useful as
immunosuppressive or immunomodulatory agents for the
treatment and/or prevention of organ transplantation
rejection, graft versus host disease, autoimmune
diseases such as rheumatoid arthritis (RA), multiple
25 sclerosis (MS), myasthenia gravis (MG) and systemic
lupus erythematosus (SLE), psoriasis and other chronic
inflammatory diseases.

The 3-phenyl-5,6-dihydrobenz[c]acridine-7-
carboxylic acid compounds of this invention can be used
30 alone or in combination with other known
immunosuppressive agents, such as cyclosporin A (CSA),
azathioprine (AZA) corticosteroids, OKT3, FK506,
mycophenolic acid or the morpholinethylester thereof,
15-deoxyspergualin, rapamycin, mizoribine, misoprostol;
35 or anti-interleukin-2 receptor antibodies, for the

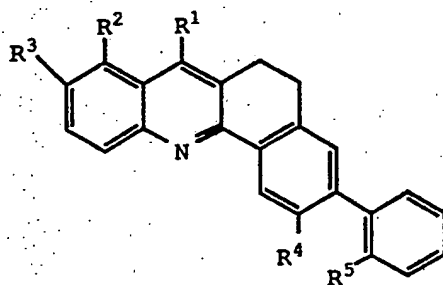
treatment and/or prevention of immunomodulatory disorders. When used in combination with other known agents, a lower dose of each agent can be used, with an associated lower incidence of side effects.

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SUMMARY OF THE INVENTION

According to the present invention there are provided methods of treating and/or preventing immunologic disorders including autoimmune disease (such as RA, SLE, MS and MG), organ transplantation rejection, graft versus host diseases, psoriasis or other chronic inflammatory diseases in a mammal, said method comprising administering to the mammal an immunosuppressive effective amount of a compound of the formula:

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(I)

or a pharmaceutically acceptable salt thereof,
wherein:

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R^1 is CO_2H , CO_2Na , CO_2K or CO_2R^6 ;

R^2 and R^3 independently are H, F, Cl, Br, I, CH_3 , CH_2CH_3 , CF_3 or $\text{S(O)}_m\text{R}^7$;

25

R^4 and R^5 independently are H, or taken together are S, with the proviso that when R^1 is CO_2Na then R^3 is not F;

R^6 is $(\text{CH}_2)_n\text{NR}^8\text{R}^9$;

R^7 is alkyl of 1 to 5 carbon atoms optionally substituted with 1 or 2 of F, Cl and Br;

R⁸ and R⁹ independently are H or alkyl of 1 to 3 carbon atoms;

m is 0 to 2; and

n is 2 to 4.

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Additionally provided is the above-described method wherein the compound is administered in combination with a non-steroidal anti-inflammatory drug or in combination with at least one immunosuppressive agent selected from the group consisting of cyclosporin A, azathioprine, prednisone, OKT3, FK506, mycophenolic acid or the morpholinethylester thereof, 15-deoxyspergualin, rapamycin, mizoribine, misoprostol and anti-interleukin-2 receptor antibodies. Non-steroidal antiinflammatory agents useful in the present invention include, but are not limited to, aspirin, ibuprofen, naproxen (sodium), indomethocin, suprofen, sulindac, piroxicam and tolmetin sodium.

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Current recommended therapy for the prevention of organ transplantation rejection and related disorders, including graft versus host disease, traditionally involves patient treatment with cyclosporin A and adjunct therapy with corticosteroids and other immunosuppressive drugs (Jacobs and Elgin "Cyclosporin A, Current Status, Including the Cape Town Experience" in Immune Modulation Agents and Their Mechanisms, ISBN 0-8247-7178-8, 1984, pp 191-228; Transplantation and Clinical Immunology, Volume XX, Combined Immunosuppressive Therapy in Transplantation ISBN 0-444-81068-4, 1989). Significant clinically observed toxicities are associated with cyclosporin A (nephrotoxicity) and azathioprine (hepatotoxicity).

Our results show that 3-phenyl-5,6-dihydrobenz[c]acridine-7-carboxylic acids and their derivatives should be useful when used alone or included with

current regimens of drug therapy for the prevention of organ transplantation rejection and related complications as well as other immunologic diseases.

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Preferred Embodiments

Preferred compounds useful in the method of the present invention are those compounds of Formula (I) wherein:

- (a) R¹ is CO₂H or CO₂Na; and/or
- 10 (b) R² is H or Cl; and/or
- (c) R³ is H, F, or Cl.

More preferred compounds useful in the method of the present invention are preferred compounds wherein:

- (a) R² is H; and/or
- 15 (b) R³ is H or F.

Specifically preferred compounds useful in the method of the present invention are:

- (a) 5,6-Dihydro-3-phenylbenz[c]acridine-7-carboxylic acid, or a sodium salt;
- 20 (b) 5,6-Dihydro-9-fluoro-3-phenylbenz[c]acridine-7-carboxylic acid, or a sodium salt;
- (c) 6,7-Dihydro-3-fluoro-[1]-benzothieno[2',3':4,5]benz[1,2-[c]acridine-5-carboxylic acid, or a sodium salt; and
- 25 (d) 6,7-Dihydro-[1]-benzothieno[2',3':4,5]-benz[1,2-c]acridine-5-carboxylic acid, or a sodium salt.

Detailed Description of the Invention

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The 3-phenyl-5,6-dihydrobenz[c]acridine-7-carboxylic acids and related compounds useful in this invention are described in and prepared by methods set forth in copending, commonly assigned U.S. Patent Applications Serial Number 07/301,379 and Serial Number

07/473,507, the disclosure, synthesis, and synthetic examples of which are hereby incorporated by reference.

The isolation of the FK506 natural product is described in European Patent Application publication
5 number 240,773, published 10/14/87 and the chemical synthesis of FK506 is described in Jones et al. (1989) J. Am. Chem. Soc. 111:1157-1159.

The preparation of azathioprine is described in U.S. Patent 3,056,785 issued to Burroughs Wellcome.
10 Azathioprine is available as Imuran®, for which the product information, including dosage and administration, is given in Physicians' Desk Reference 44th Edition, 1990, pp 777-778.

The preparation of cyclosporin A is described in
15 U.S. Patent 4,117,118 issued to Sandoz. Cyclosporin A is available as Sandimmune®, for which the product information, including dosage and information, is given in Physicians' Desk Reference, 44th Edition, 1990, pp 1950-1952.

20 The preparation of prednisone is described in U.S. Patents 2,897,216 and 3,134,718 issued to Schering. Prednisone is available commercially from several manufacturers (see generally, Physicians' Desk Reference, supra).

25 Murine monoclonal antibody to the human T3 antigen (herein referred to as OKT3) is available as Orthoclone OKT®3, for which the product information, including dosage and administration and references to methods of preparation, is given in PDR, 1990, pp 1553-1554.

30 The preparation of mycophenolic acid is described in British patents 1,157,099; 1,157,100 and 1,158,387 to ICI.

15-deoxyspergualin is a derivative of spergualin discovered in culture filtrates of the bacterial strain
35 BGM 162-aFZ as reported in Ochiai, T., Hoi, S.,

Nakajimak, et al. Prolongation of Rat Heart Allograft Survival by 15-deoxyspergualin, 5. Antibiot. (Tokyo) 1987; 40:249.

5 Mizoribine is described in U.S. Patent 3,888,843 issued to Toyo Jozo.

Misoprostol, a prostaglandin (PGEI) analog, is described in U.S. Patent 3,965,143 assigned to Searle and U.S. Patent 4,132,738 assigned to Miles.

10 Rapamycin is described in U.S. Patents 4,650,803; 4,316,885; 4,885,171; 3,993,749 and 3,929,992 all assigned to Ayerst.

Antibodies to the IL-2 receptor protein are described in U.S. Patents 4,578,335 and 4,845,198 (Immunex) and USSN 07/341,361 and U.S. Patent 4,892,827
15 issued to Pastan et al.

Utility

Results of the biological tests described below establish that the compounds of this invention have the
20 ability to suppress/inhibit the contact sensitivity response to 2,4-dinitrofluorophenyl (DNFB) in mice and the human mixed lymphocyte reaction.

Contact Sensitivity Response to DNFB in Mice

Balb/c female mice (\approx 20 g; Charles River) were
25 sensitized on the shaved abdomen with 25 μ l of 0.5% 2,4-dinitrofluorobenzene (DNFB, Eastman Kodak Co.) in a vehicle of 4:1 acetone:olive oil on days 0 and 1. Mice were ear challenged with 20 μ l of 0.2% DNFB in a vehicle of 4:1 acetone:olive oil on day-5. An identical segment
30 of the ear was measured immediately before challenge and 24 hours later with an engineer's micrometer. Ear swelling was expressed as the difference in ear thickness before and after challenge in units of 10^{-4} inches \pm SEM. Percent suppression was calculated as:

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$$\% \text{ Suppression} = 1 - \frac{\text{compound treated-negative control}}{\text{positive control-negative control}} \times 100$$

Compounds were administered orally from day-2 through
5 day-6 and were prepared in 0.25% Methocel® (Dow Chemical
Co.). Control animals received only vehicle (0.25%
Methocel®). Negative controls were not sensitized on
days 0 and 1 but were ear challenged on day-5. Ten mice
were used per group. Results with compounds of the
10 present invention are shown in Table 1.

Contact sensitivity to DNFB is a form of delayed-
type hypersensitivity which has been extensively studied
to gain an understanding of the regulation of
immunologic processes (Claman et al. (1980),
15 Immunological Rev. 50:105-132). This reaction is
mediated by T lymphocytes that become sensitized to
antigen by proliferating and developing into mature
effector cells (Claman et al. (1980), Immunological Rev.
20 50:105-132). This cell-mediated immune response (T-cell
mediated immunity) is central to many disease states
such as organ transplantation rejection and graft versus
host disease (Benacerraf and Unanue (1979), Textbook of
Immunology, Williams & Wilkins Co.; Eisen (1980),
Immunology. An Introduction to Molecular and Cellular
25 Principles of the Immune Responses, Harper & Row, Inc.;
Loveland and McKenzie (1982), Immunology 46:313-320;
Gallin et al. (1988), Inflammation, Basic Principles and
Clinical Correlates, Raven Press).

The contact sensitivity model used for this study
30 is a model system for delayed-type hypersensitivity
reactions which have been linked to the disease
pathology associated with organ transplantation
rejection, graft versus host disease, MS, MG, SLE, RA,
psoriasis and other chronic inflammatory diseases and
35 autoimmune diseases for which the T-cell is pivotal to
mounting an immune or autoimmune response.

A representative 3-phenyl-5,6-dihydrobenz[c]acridine-7-carboxylic acid compound of the method of the invention, 5,6-dihydro-9-fluoro-3-phenylbenz-[c]-acridine-7-carboxylic acid, sodium salt (Example 12 of U.S. Patent Application Serial Number 07/301,379); herein referred to as Example 12), was tested in the DNFB contact sensitivity model (Table 1).

Table 1

10

Treatment	Dose (mg/kg)	Ear Swelling ^a (units ± SEM)	%
			Suppression
Negative	Vehicle	2.30±0.86	-
15 Positive	Vehicle	57.17±3.51	0
Cyclosporin A	20.0	41.50±5.85	28.55
20 Example 12	20.0	2.44±1.62	99.75

a Increase in ear thickness from day 5 to day 6, unit = 10^{-4} inches

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The present results show that Example 12 and related 3-phenyl-5,6-dihydrobenz[c]acridine-7-carboxylic acid derivatives have immunosuppressive activity and as such should be useful when included alone or in combination with other drugs used in current regimens of drug therapy for the prevention of organ transplantation rejection, autoimmune disease, chronic inflammatory disease, and related disorders (Jacobs and Elgin (1984) "Cyclosporin A, Current Status, Including the Cape Town Experience", in Immune Modulation Agents and Their Mechanisms, pp 191-228; Transplantation and Clinical

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Immunology, Volume XX, Combined Immunosuppressive
Therapy in Transplantation ISBN 0-444-81068-4, 1989).

Human Mixed Lymphocyte Reaction

5 Blood was obtained by venipuncture from two
nonrelated human donors. Peripheral blood mononuclear
cells (PBMC) were isolated from these samples by using
the Leuco Prep procedure (Becton-Dickinson). PBMC were
10 washed twice in phosphate buffered saline (without
calcium and magnesium) and the separate cell isolations
were adjusted to the appropriate concentrations in media
(RPMI 1640) supplemented with 10% human AB serum and 30
µl/ml gentamicin. Cells from donor A (2×10^5) were
15 incubated with cells from donor B (2×10^5) in 96 well
round bottom microliter plates at 37°C, 5% CO₂ for 6
days. Eighteen hours prior to harvesting cells from the
plates, all wells were pulsed with 1 µCi of ³H-
thymidine. Cells from the plates were harvested on day-
6 and ³H-thymidine incorporation was determined using a
20 scintillation counter. Test results are shown in Table
2.

Table 2

	<u>Compound</u>	<u>IC₅₀ (M)</u>
25	Cyclosporin A	1.6×10^{-8}
	Example 12	6.5×10^{-8}

The human mixed lymphocyte reaction model, is an in
vitro model for transplantation rejection. The results
30 in Table 2 show that Example 12 and related compounds
are comparable to CSA the drug of choice for
transplantation rejection.

Dosage Forms

The immunosuppressive compounds (active ingredients) of this invention, can be administered to treat immunologic disorders and inflammatory diseases by any means that produces contact of the active ingredient with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals; either as individual therapeutic active ingredients or in a combination of therapeutic active ingredients. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be an immunosuppressive effective amount of active ingredient and will, of course, vary depending upon known factors such as: the pharmacodynamic characteristics of the particular active ingredient, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms; kind of concurrent treatment, frequency of treatment; and the effect desired. Usually a daily dosage of active ingredient can be about 0.1 to 400 milligrams per kilogram of body weight. Ordinarily, 1 to 200 and preferably 10 to 50 milligrams per kilogram per day is effective to obtain desired results, provided, that when the compounds of the present invention are used in combination with one or more known immunosuppressive agents, the dose of each agent should be reduced.

Dosage forms (compositions) suitable for internal administration contain from about 1.0 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will

ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions, it can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain preferably a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can

contain preservatives, such as benzaalkonium chloride, methyl- or propyl-paraben, and chlorbutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard
5 reference text in this field.

Useful pharmaceutical dosage forms for administration of the compounds of this invention can be illustrated as follows:

10 Capsules:

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 175 milligrams of lactose, 24 milligrams of talc, and 6
15 milligrams magnesium stearate.

A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active
20 ingredient. The capsules are washed and dried.

Tablets:

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100
25 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystal line cellulose, 11 milligrams of cornstarch and 98.8 milligrams of lactose. Appropriate coatings may be applied to
30 increase palatability of delay absorption.

Injectable:

A parenteral composition suitable for administration by injection is prepared by stirring 1.5%
35 by weight of active ingredient in 10% by volume

propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

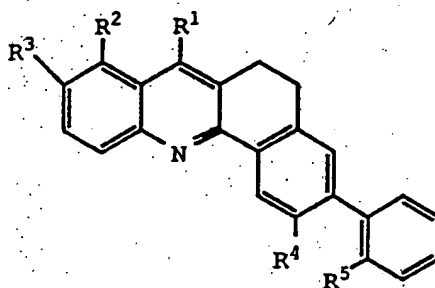
Suspension:

- 5 An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 200 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.
- 10

- The same dosage forms can generally be used when the compounds of this invention are administered stepwise in conjunction with another therapeutic agent. When drugs are administered in physical combination, the
- 15 dosage form and administration route should be selected for compatibility with both drugs.

WHAT IS CLAIMED IS:

1. A method of treating an autoimmune disease, psoriasis, graft versus host disease, organ transplantation rejection, or a chronic inflammatory disease in a mammal comprising administering to the mammal in an amount effective for the treatment of a desired aforesaid disease a compound having the formula:



(I)

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or a pharmaceutically acceptable salt thereof, wherein:

R^1 is CO_2H , CO_2Na , CO_2K , or CO_2R^6 ;

R^2 and R^3 independently are H, F, Cl, Br, I, CH_3 , CH_2CH_3 , CF_3 , or $\text{S(O)}_m\text{R}^7$;

15

R^4 and R^5 independently are H, or taken together are S with the proviso that when R^1 is CO_2Na then R^3 is not F;

R^6 is $(\text{CH}_2)_n\text{NR}^8\text{R}^9$;

20

R^7 is alkyl of 1 to 5 carbon atoms optionally substituted with 1 or 2 of F, Cl and Br;

R^8 and R^9 independently are H or alkyl of 1 to 3 carbon atoms;

m is 0 to 2; and

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n is 2 to 4.

2. A method of Claim 1 wherein R^1 is CO_2H or CO_2Na .

3. A method of Claim 1 wherein R^2 is H or Cl.

4. A method of Claim 1 wherein R^3 is H, F or Cl.

5. A method of Claim 1 wherein R^1 is CO_2H or CO_2Na ,

R^2 is H or Cl, and R^3 is H, F or Cl.

6. A method of Claim 5 wherein R^2 is H.

7. A method of Claim 5 wherein R^3 is H or F.

8. A method of Claim 1 wherein R^2 is H and R^3 is H or F.

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9. The method of Claim 1 wherein the compound of formula (I) is 5,6-dihydro-3-phenylbenz[c]acridine-7-carboxylic acid, or a sodium salt thereof.

10. The method of Claim 1 wherein the compound of formula (I) is 5,6-dihydro-9-fluoro-3-phenylbenz[c]acridine-7-carboxylic acid, or a sodium salt thereof.

11. The method of Claim 1 wherein the compound of formula (I) is 6,7-di-hydro-3-fluoro-[1]-benzothieno[2',3':4,5]benz[1,2-[c]acridine-5-carboxylic acid, or a sodium salt thereof.

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12. The method of Claim 1 wherein the compound of formula (I) is 6,7-dihydro-[1]-benzothieno[2',3':4,5]benz[1,2-c]acridine-5-carboxylic acid, or a sodium salt thereof.

13. The method of Claim 1 wherein the compound of formula (I) is administered in combination with at least one immunosuppressive agent selected from the group consisting of cyclosporin A, azathioprine, a corticosteroid, OKT3, FK506, mycophenolic acid or the morpholinethylester thereof, 15-deoxyspergualin, rapamycin, mizoribine, misoprostol, or anti-interleukin-2 receptor antibodies.

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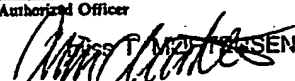
14. The method of Claim 1 wherein the compound of formula (I) is administered in combination with a nonsteroidal antiinflammatory drug.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/04381

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 31/47		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
P,A	EP,A,0380038 (E.I. DU PONT DE NEMOURS AND COMPANY) 1 August 1990, see abstract; claims 1-10 ---	1-12
A	EP,A,0339484 (E.I. DU PONT DE NEMOURS AND COMPANY) 2 November 1989, see abstract; page 2, second paragraph; claims 1-3 ---	1-12
A	EP,A,0339485 (E.I. DU PONT DE NEMOURS AND COMPANY) 2 November 1989, see abstract; claims 1-11 ---	1-12,14
A	EP,A,0305952 (AMERICAN CYANAMID CO.) 8 March 1989, see page 2, paragraph 1 --- -/-	1-12
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
08-10-1991		13. 12. 91
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	<p>Ernst Mutschler: "Arzneimittelwirkungen", 5th Edition 1986, Wissenschaftliche Verlagsgesellschaft mbH (Stuttgart, DE), see page 654, paragraph 9.3.4 to page 656</p> <p>-----</p>	13

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers
Authority, namely: because they relate to subject matter not required to be searched by this
Remark: Although claims 1-14 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claim numbers
because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers
because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9104381
SA 49725

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 06/12/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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